

Remarks

Claims 1-8 are pending in the application, claims 21-22 have been canceled, and claims 23-34 have been withdrawn from consideration by the Examiner. Applicants reserve the option to further prosecute the same or similar claims in the instant or in a subsequent patent application.

Claim 1 has been amended. No new matter has been added. Amendment of claims should in no way be construed to narrow their scope or as an acquiescence to any of the Examiner's rejections. The amendments to the claims are being made solely to expedite prosecution of the present application. Applicants reserve the option to further prosecute the same or similar claims in the instant or in a subsequent patent application.

Claims 23-34 have been withdrawn by the Examiner as being directed to an additional, non-elected invention. Applicants respectfully traverse this additional restriction and withdrawal of the claims. The Examiner, in the original restriction requirement, found two inventions, a "crystal of RNA polymerase" and a "method of making." Applicants urge that a "crystal of a core RNA polymerase" is in the same invention classification as a "crystallized polypeptide" comprising, for example, a polypeptide having the sequence of the core RNA polymerase, SEQ ID NO: 1. The Examiner argues that the latter crystallized composition comprises multiple subunits, homologs, or other derivatives, whereas the originally claimed crystal of a core RNA polymerase does not. The claims themselves undermine the Examiner's argument. For example, claim 5, which claims the originally claimed crystal, clearly indicates the crystal has multiple subunits, because it recites that the crystal "comprises a β' subunit, a β subunit, and a pair of α subunits." Thus, claims 23-34 are drawn to the same invention as elected in the Applicants' response to the restriction requirement, filed on April 3, 2003.

Further, for a restriction requirement to be valid, the Examiner must establish that the search and examination of the entire application cannot be made without serious burden. If the search and examination of an entire application can be made without serious burden, the examiner must examine it on the merits, even though it includes claims to independent or distinct inventions. (M.P.E.P. § 803). Applicants respectfully submit that a search and examination of the claimed crystals of a core RNA polymerase would also entail searching for crystalline compositions comprising core polymerases having SEQ ID NO: 1, as well as homologs and

subunits thereof, posing no serious burden. Accordingly, Applicants respectfully request examination of claims 23-34.

Rejection of claims 1-8 under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 1-8 under 35 U.S.C. § 112, first paragraph as unenabled because the specification allegedly does not disclose crystals of RNAP from any eukaryote. Applicants have amended claim 1 so that it no longer recites "eukaryote." Amendment of claims should in no way be construed to narrow their scope or as an acquiescence to any of the Examiner's rejections. The amendments to the claims are being made solely to expedite prosecution of the present application.

By such amendment, Applicants urge that the instant rejection for lack of enablement has been rendered moot, and respectfully request the withdrawal of the rejection.

Rejection of claims 1-3 and 5-8 under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claims 1-3 and 5-8 under 35 U.S.C. § 112, first paragraph as allegedly unenabled because the specification, while being enabling for the crystal of *Thermus aquaticus* bacterial core RNA polymerase, does not provide enablement for a crystal of any other bacterial or other source core RNA polymerase suitable for the same resolution determination. The Examiner argues that the only crystal demonstrated to enable the required X-ray diffraction is the *Thermus aquaticus* bacterial core RNA polymerase crystal, and that although there is general guidance regarding preparation of core RNA polymerase crystals from other bacterial sources, there is no clear teaching on how to arrive at crystals with the required X-ray quality.

Applicants respectfully point the Examiner's attention to MPEP § 2164.01, which cites United States v. Teletronics, Inc., 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. Cir. 1988): "The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." Further, Application also respectfully point the Examiner's attention to MPEP § 2164.02, which states in relevant part: "[t]he presence of only one working example should never be the sole reason for rejecting claims as being broader than the enabling disclosure, even though it is a factor to be considered along with all the other factors."

Although the Examiner points to the Service and Drenth references as allegedly demonstrating that obtaining single crystals is the least understood step in X-ray structural analysis and that the science of obtaining protein crystals is uncertain, such references do not refute the notion that screening a matrix of iterative conditions to afford a crystal is anything but routine. In fact, both references note that such experimentation is routine in the art, and has indeed become easier as robotics and computer software enable researchers to screen extremely large numbers of conditions. Therefore, Applicants respectfully submit that the disclosed preparations of high quality crystals of *Thermus aquaticus* bacterial core RNA polymerase as well as several heavy metal atom derivatives thereof, are sufficient to enable the preparation of other RNA polymerase crystals without undue experimentation when coupled with the general guidance provided in the specification as well as techniques known in the art for the preparation of high quality crystals. Such preparation may, for example, entail screening a fairly large number of conditions which are variations on the conditions disclosed in the instant specification. As noted in Ex parte Forman, 230 USPQ 546, 547 (Bd. Pat. App. & Int. 1986) and In re Brandstadter, 484 F.2d 1395, 1407, 179 USPQ 286,294-295 (CCPA 1973), a considerable amount of experimentation is permissible, if it is merely routine or if the specification in question provides a reasonable amount of guidance. Screening a matrix of iterative variations on a condition known to afford a crystal is routine in the crystallography art. Therefore, Applicants respectfully urge that the disclosure in the specification is sufficient to allow one of skill in the art to practice the claimed invention without undue experimentation, and request withdrawal of the rejection.

Further, although the Examiner points out that protein crystallization is an unpredictable art, Applicants urge that, in light of the other *Wands* factors, such as the amount of experimentation required, the scope of the claims (now drawn only to prokaryotic species), the existence of at least one working example in the specification, the general guidance provided in the specification, and the state of the prior art, the claimed invention is enabled by the specification.

Applicants respectfully request the withdrawal of the instant rejection.

Rejection of claim 6 under 35 U.S.C. § 112, first paragraph

The Examiner has rejected claim 6 under 35 U.S.C. § 112, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s) at the time the application had possession of the claimed invention because the specification does not demonstrate a crystal of a core RNA polymerase having a ω subunit. Applicants have pointed out that the crystal of the *Thermus aquaticus* bacterial core RNA polymerase disclosed in the specification contains a ω subunit, as noted, for example, at pages 48 in lines 26-27, page 53 in lines 24-29, and page 54 in Table 2 and lines 1-2. The Examiner asserts that the portions of the specification to which Applicants refer merely “address a possible presence of the subunit in certain RNAP preparations.”

Applicants respectfully submit that the Examiner has incorrectly interpreted the specification and results described therein. Page 48 describes an analysis of the RNAP preparation from which the crystals were prepared. The analysis shows that the fourth polypeptide, or ω subunit, was present in the preparation. Although the specification states that this polypeptide was tentatively *named* the ω subunit, the specification does *not* state that the polypeptide was tentatively present. Indeed, the structural analysis of the crystals proved that the ω subunit was present in the crystal, as described on page 54. The resolution of the crystal was even sufficient to allow the characterization of the contacts that the ω subunit makes with other subunits - see, for example, lines 7-11 on page 58.

Therefore, Applicants respectfully request the withdrawal of the rejection of claim 6 for lack of enablement.

Rejection of claims 1-3, and 5-7 under 35 U.S.C. § 102(b) over Polyakov, et al

The Examiner has maintained his rejection of claims 1-3, and 5-7 under 35 U.S.C. § 102(b) as anticipated by Polyakov, et al. (Cell, 83, 365-373, 1995), which allegedly teaches crystals of bacterial RNA polymerase having $\alpha\alpha\beta\beta'$ subunits. Examiner asserts, citing In re Pearson (494 F.2d 1399, 181 USPQ 641 (CCPA 1974)) that the claimed limitation regarding intended use for determination of atomic coordinates is an intended use limitation, which does not impart patentability to product claims where the product is otherwise anticipated by the prior art. Applicants respectfully point out that In re Pearson held that intended use limitations could

be used to distinguish a composition from the prior art so long as “such terms ... define, indirectly at least, some characteristic not found in the old composition.” (In re Pearson, at 1403)

Applicants assert that the present limitation “effectively diffracts X-rays for the determination of the three-dimensional atomic coordinates to a resolution of better than 3.5 Angstroms” is a limitation that defines a characteristic not found in the Polyakov crystal – the ability of the presently claimed crystals to diffract X-rays for the determination of three-dimensional atomic coordinates to a resolution of better than 3.5 Angstroms. The Polyakov crystal preparations are entirely different compositions that are simply not capable of diffracting X-rays for the determination of three-dimensional atomic coordinates to the claimed resolution. The two-dimensional crystals of Polyakov, et al were prepared on positively charged lipid layers, a technique for preparing *two-dimensional crystals* suitable for electron microscopy, rather than a technique for preparing three-dimensional crystals suitable for high-resolution structure determination by x-ray crystallography. Applicants point to a commentary (attached as Exhibit A) by one of the inventors in the instant application, Seth A. Darst, that was published in the July 7, 1998 issue of the *Proceedings of the National Academy of Sciences*. In this commentary, Darst distinguishes between 2D crystals, which are specimens for electron microscopy analysis, and 3D crystals, which are suitable for x-ray analysis. According to the commentary, electron microscopic analysis of 2D crystals has been used to obtain structural information on proteins that could not be analyzed by x-ray analysis *because 3D crystals of such proteins could not be prepared*. The presently claimed crystal is distinguishable from the crystal of Polyakov, et al because it defines a characteristic not found in the Polyakov, et al crystal, that is, a particular composition and particular dimensions that allow for its use in the determination of three-dimensional atomic coordinates by x-ray crystallography.

Hence, Applicants respectfully request withdrawal of the present rejection.

Conclusion

In view of the foregoing amendments and remarks, Applicants submit that the pending claims are in condition for allowance. Early and favorable reconsideration is respectfully solicited. The Examiner may address any questions raised by this submission to the undersigned

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at 617-832-1000. Any other fee required for timely consideration of this application be charged to Deposit Account, No. 06-1448 (Ref. IPT-011.02).

Respectfully submitted,

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